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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,970	08/10/2001	Ashok Amin	AMIN4A	4363

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EXAMINER
WORTMAN, DONNA C

ART UNIT	PAPER NUMBER
1648	7

DATE MAILED: 09/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/925,970	AMIN ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 1-6 as originally filed remain pending and under examination.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 4 are indefinite in reciting "p75:FC inhibitor" which terminology is confusing since it is not clear whether "p75:FC inhibitor" is a type of inhibitor, or is that which is to be inhibited.

Applicant has asserted that [0014] provides a definition for "p75:FC inhibitor," and states that etanercept and infliximab inhibit p75:FC.

These remarks have been considered but not found persuasive, since etanercept is a fusion protein consisting of the ligand binding portion of the p75 tumor necrosis factor receptor linked to a human IgG1 Fc (specification, [0006]) that is commonly referred to as "p75:Fc." Claims 3 and 4 remain indefinite since it appears that Applicant uses a definition that is not the same as the conventional meaning for etanercept, which inhibits tumor necrosis factor binding to its receptor.

With respect to the rejection of claims 1, 3, and 5 under 35 U.S.C. 112, second paragraph, as previously offered, Applicant has asserted that the exemplified compounds (etanercept and infliximab) are encompassed, that compounds that neutralize the effects of TNF alpha are encompassed, and that the mechanism by which neutralization is accomplished is immaterial.

Applicant's comments have been considered and claims 1, 3, and 5 continue to be given their broadest reasonable interpretation based on the language recited and Applicant's comments.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record.

Applicant has argued (1) that no reason has been given that one could not extrapolate from the results with one patient that administration of an anti-TNF alpha compound would improve viral levels in patients suffering from hepatitis; (2) that the present inventors have discovered that inhibiting TNF alpha reverses the evidence of hepatic inflammation associated with active hepatitis; (3) that a specification that contains a teaching of the manner and process of making an invention in terms which correspond to the scope of those used in describing and defining the subject matter sought to be patented must be taken in as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein; (4) that the present application provides an example of successful human treatment, and (5) that one skilled in the art can appreciate that administration of a compound that neutralizes the effects of

secreted TNF-alpha can be used to treat hepatitis. Applicant has argued (6) that Campbell et al., of record, provides additional evidence that anti-TNF alpha compounds are useful in treating hepatitis.

Applicant's arguments have been considered but not found persuasive. With respect to point (1), Applicant is relying on limitations, improving of viral levels, that are not found in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). With respect to points (2)-(5), the teachings of the specification, including the observation of the condition of a single patient after treatment with a single compound, do not correspond to the scope of the subject matter sought to be patented. While Campbell et al. administered infliximab for the treatment of Crohn's disease to a patient with chronic hepatitis C, Campbell reported the result of the treatment with respect to the patient's hepatitis C as "no worsening." "No worsening" is hardly the same as successful treatment.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by The Merck Manual of Diagnosis and Therapy (Beers et al., Eds., Seventeenth Edition, published by Merck Research Laboratories, 1999) pages 384-386, of record, for reasons of record.

Applicant has argued that the cited reference does not disclose or suggest that anti-TNF alpha compounds should be used in treating hepatitis; that corticosteroids are said to be contraindicated, and that interferon-alpha initially suppresses inflammation and suppresses viral replication. Claim 1 is not limited to viral hepatitis, and the Merck Manual at page 386 states that "autoimmune hepatitis is best treated with corticosteroids"; claim 1 is anticipated. Claim 2 recites treatment of, *inter alia*, hepatitis B and hepatitis C. The Merck Manual discloses that treatment of hepatitis B and hepatitis C with interferon-alpha results in decreased inflammatory activity. Inflammatory activity is an effect of TNF alpha, and Applicant has stated that compounds that neutralize the effects of TNF alpha are encompassed, and that the mechanism by which neutralization is accomplished is immaterial. Consequently, claims 1 and 2 encompass interferon treatment of hepatitis B and C and claims 1 and 2 are anticipated.

Certain art made of record and not relied upon is considered pertinent to applicant's disclosure. All four documents are cited on PTO 892, attached.

Peterson et al. (Arthritis Rheum. 44(9):Suppl., November 2001, page S78), in summarizing the treatment of nine patients with rheumatoid arthritis and chronic hepatitis C with either etanercept or infliximab, report that "LFT and HCV viral load measurements are usually not affected by short-term use of TNF-α antagonists."

Tilg et al. (Hepatology Vol. 34, No. 4, Pt. 2, October 2001, p. 696A) discloses treatment of two patients HCV-positive severe alcoholic hepatitis with infliximab. One patient remained HCV RNA negative and HCV antibody positive after treatment, and

the second patient showed decreased liver inflammation, interpreted by the authors as an improvement in alcoholic hepatitis, but also showed an increase in HCV viral replication. The authors concluded that "The effect of TNF-neutralization in HCV positive liver disease warrants further study."

Hayat et al. (Clinical Immunology Vol. 103, No. 3, Part 2, Supp., June 2002, p. S80) discloses the effect of infliximab therapy for rheumatoid arthritis in a patient with chronic hepatitis C. After 6 weeks of infliximab the patient was started on interferon and ribavirin. HCV viral load increased 1.69×10^7 copies/ml 1 week post treatment and then returned to pretreatment baseline 2.96×10^6 copies/ml. There was no change in the level of pro- and anti-inflammatory cytokines and liver function tests with therapy.

Biancone et al. (Gastroenterology Vol. 122, No. 2, pp. 593-594) discloses the use of immunomodulatory drugs in Crohn's disease patients with hepatitis B or C virus Infection. See, e.g., Table 1, Pt. 8: treatment with infliximab resulted in no clinical effect on liver disease.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032. The examiner can normally be reached on Monday-Thursday, 7:30-5:00 and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw
September 27, 2002